Exercise increases prolactin-receptor expression on human lymphocytes

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Dohi, Keiichiro, William J. Kraemer, and Andrea M. Mastro. Exercise increases prolactin-receptor expression on human lymphocytes. J Appl Physiol 94: 518–524, 2003.—Plasma prolactin has been shown to increase during exercise stress; the immune system is responsive to prolactin and affected by stress. Therefore, this study was undertaken to investigate the effects of acute graded, maximal treadmill exercise on prolactin-receptor expression by lymphocytes. Eight healthy men underwent one exercise and one nonexercise session. Blood was sampled immediately before and after the exercise. On the day of the nonexercise session, two resting blood samples were obtained at the same times as the exercise session samples to act as baseline data. Plasma prolactin concentrations were significantly elevated in response to exercise and correlated positively with total prolactin-receptor expression per B lymphocyte. An increase in total prolactin-receptor expression per B lymphocyte in response to exercise also was observed. In addition, exercise significantly increased the total number of circulating lymphocytes expressing prolactin receptor as well as the total number of circulating B lymphocytes. These data support the idea that exercise may enhance the interaction between immune target cells and prolactin, a stress hormone capable of enhancing immune function.

stress hormones; B lymphocytes; immune-neuroendocrine interactions; treadmill exercise

PROLACTIN IS A PEPTIDE HORMONE secreted by the anterior pituitary gland. In addition to its regulatory function in the reproductive system, such as in lactation, prolactin has been shown to stimulate cells of the immune system. For instance, prolactin can enhance antibody production, lymphocyte proliferation, natural killer (NK) cell activity, and macrophage phagocytosis (7, 31, 38). It also may be important in immune cell development (8). Because of its immune-enhancing ability, prolactin has received attention as a candidate therapeutic agent for patients with immunodeficiency after bone marrow transplants or cancer radiation and/or chemotherapy (reviewed in Ref. 17).

Interestingly, substantial evidence indicates that prolactin secretion increases and immune cells are stimulated after stress (10, 21). Prolactin may counteract other immunosuppressive, stress-responsive hormones (5, 6) such as glucocorticoids. In response to acute aerobic exercise, the concentrations of circulating leukocytes as well as plasma prolactin levels are elevated (20, 27, 34). Thus greater numbers of immune cells could interact with increased levels of prolactin in the blood during exercise, leading to an overall stimulation of the immune system. Animal studies support this possibility (35). For example, Ortega et al. (35) demonstrated that exercise-induced, prolactin elevation in mice was associated with enhanced macrophage chemotaxis and phagocytosis.

At present, limited information is available regarding human leukocytes and prolactin in response to exercise. The mechanisms that regulate the immune system during exercise appear to be quite complex because many biological substances (e.g., hormones, cytokines) also are secreted into the blood (23, 34). However, it may be possible to begin to understand a role for prolactin in immune cell function by analyzing prolactin-receptor expression on human lymphocytes under conditions known to increase plasma prolactin concentrations (e.g., exercise stress). To date, prolactin-receptor expression on human immune cells in response to exercise stress has not been examined despite the fact that prolactin-receptor expression is essential for the action of prolactin on its target cells (5, 6, 18). Stimulation of the immune system via the neuroendocrine system is likely mediated through these ligand–receptor interactions (6). Animal studies indicate that high concentrations of prolactin increased prolactin-receptor expression on target tissues such as liver, lung, hypothalamus, and brain (2, 30). Thus we hypothesized that acute aerobic exercise would increase prolactin-receptor expression by the target immune cells among the blood leukocytes.

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METHODS

Subjects

Eight men between the ages of 18 and 29 yr were recruited and determined by a physician to be healthy for the participation in this study. Each subject was a non-smoker and had been regularly engaged in aerobic exercise at least three times per week over the past year. The average characteristics of the subjects were 24.5 ± 4.7 (SD) yr of age, 178.2 ± 10.7 cm height, 76.1 ± 11.6 kg weight, 9.4 ± 3.5% body fat, and 51.5 ± 7.4 ml·kg⁻¹·min⁻¹ maximal \( V_{\text{O2 max}} \). After the investigators carefully explained the study procedures, each individual who agreed to participate signed an informed consent form approved by the Institutional Review Board for the Use of Human Subjects at The Pennsylvania State University.

Experimental Design

Each subject underwent two sessions (1 exercise session and 1 nonexercise session) separated by at least 1 wk. The order of the test session was randomized. The first session was always started between 9:00 and 10:00 AM to control for variations in the circadian periodicity of prolactin secretion. In the first session, each subject was screened by a physician for participation into this study. The physical examination included the performance of a baseline 12-lead electrocardiography (Marquette, Milwaukee, WI), measurement of resting blood pressure, and determination of skinfold thickness. Body density and percent body fat were calculated as previously described (9, 25).

On the day of the exercise testing session, a graded exercise on a treadmill (Sensormedics, Yorba Linda, CA) was conducted (1). Because high-intensity exercise is known to elevate plasma prolactin concentrations, a maximal exercise test was used for this study (15, 27). A blood sample totaling 25 ml was obtained immediately before and after the treadmill test. All blood samples were obtained by using a standard sterile venipuncture technique with 20-gauge needle and vacutainer (Vacutainer Systems, Becton Dickinson, Franklin Lakes, NJ). Each subject exercised until voluntary exhaustion on a treadmill at a constant rate [8.3 ± 1.0 (SD) miles/h] with a 2.5% increase in grade every 2 min. The duration of the run was 13.6 ± 1.8 (SD) min. During the test, heart rate was monitored continuously (Polar heart rate monitor, Polar CIC, Port Washington, NY), and blood pressure and ratings of perceived exertion (6 to 20 scale) were measured every 2 min. All metabolic data were acquired via the Sensormedics Vmax229 system (Sensormedics). Before each test, \( V_{\text{O2}} \) and \( CO_2 \) analyzer were calibrated with standard gases. The \( CO_2 \) gas consumption data were obtained every 20 s throughout the test.

On the day of the nonexercise session, two resting blood samples were obtained at the same times as the exercise session samples to act as baseline data; the time of blood sampling was consistent between exercise and nonexercise testing sessions. On the basis of a history of administering the maximum exercise test at The Pennsylvania State General Clinical Research Center, where the studies were carried out, we assumed that the test duration would be ~15 min (actual was 13.6 ± 1.8 min). We allowed an additional 10 min for instructions, measuring blood pressure, and inserting the mouthpiece. Therefore, if the nonexercise session was the first session, subjects were instructed to relax after the first blood draw and sit quietly for 25 min until the second blood draw. The participants in this study were asked to maintain activity and dietary conditions that were identical to the prior testing sessions. These included no intensive physical exercise 1 day before each session and maintenance of a constant sleep pattern. They were instructed not to consume food, alcohol, caffeine, or any other substance for 4 h before the blood draw. Each subject recorded (on a form) the food intake and physical activity for 2 days before each session.

Blood Analyses

**Complete blood count.** Blood (4 ml) to be used for a complete blood count (CBC) was collected into a vacutainer tube containing EDTA (Vacutainer systems, Becton Dickinson) and analyzed by an automated hematology analyzer (Microdiff 16, Coulter, Miami, FL). Hemoglobin, hematocrit, and total lymphocyte concentration were obtained from the CBC analysis. B-lymphocyte concentration was calculated by multiplying the total lymphocyte concentration from the CBC by the percentage of B cells determined by immunocytochemistry and flow cytometry (Epics XL-MCL, Coulter). Hemoglobin and hematocrit data were used to measure the changes in plasma volume in response to exercise (16).

**Prolactin receptor on lymphocytes.** For the measurements of plasma prolactin and lactate, blood was collected into one 10-ml vacutainer tube containing sodium heparin and mixed gently by inversion. Approximately 3 ml of the heparinized whole blood, to be used for plasma lactate measurement, were transferred into a centrifuge tube (Corning Costar, Cambridge, MA) on ice until centrifugation for 10 min at 400 g at 4°C (CRU5000 centrifuge, International Equipment, Needham Heights, MA). The remaining heparinized whole blood was centrifuged for determination of plasma prolactin, 10 min at 1,000 g at 23°C (Centra-8R Centrifuge, International Equipment). The plasma from both preparations was collected, aliquotted into 1.5-ml Eppendorf tubes, and stored at −80°C until analysis.

The plasma prolactin concentration was determined in all the samples at the same time by an immunoradiometric assay carried out in duplicate (IRMA Diagnostic Systems Laboratories, Webster, TX). The intra-assay coefficient of variation was 4.7%, and the sensitivity was 0.1 ng/ml (0.004 nmol/l). The assay was performed by using a gamma counter with an on-line data reduction system (model 1470, EG and G Wallac, Gaithersburg, MD). The plasma lactate concentration was measured enzymatically in duplicate by using a spectrophotometer as previously described (24). The intrasample coefficient of variation was 1.3%. The plasma lactate concentrations for the exercise session averaged 1.76 ± 0.03 mmol/l for preexercise and 11.61 ± 0.70 mmol/l postexercise. For the resting session, these values were 1.76 ± 0.03 and 1.76 ± 0.04 mmol/l for preexercise and postexercise sessions, respectively.

**Prolactin receptor on lymphocytes.** To examine prolactin receptors on leukocytes, blood was collected into a 10-ml vacutainer tube including sodium heparin and mixed gently by inversion. Leukocytes were isolated by Ficoll Hypaque gradient centrifugation (Pharmacia Biotech, Uppsala, Sweden) (12). The freshly isolated leukocytes were analyzed with monoclonal antibodies and flow cytometry. A monoclonal antibody for the prolactin receptor (U5) was a generous gift from Dr. Mireille Dardenne (Hopital Necker, Paris, France). U5 is a mouse monoclonal antibody that recognizes the prolactin receptor on human leukocytes (14, 33). The antigenic domain of U5 is different from the hormone-binding site (33).

First, the leukocytes (5 × 10⁶ cells) were incubated (20 min, 4°C) with a staining solution containing 5% human serum, 5% calf serum, 2% goat serum, and 0.1% sodium azide in phosphate-buffered saline to block the Fc receptors. Next,
the leukocytes were incubated with U5 (50 μl, 10 μg) for 30 min at 4°C. After a wash with staining medium, a biotinylated secondary antibody (goat anti-mouse 50 μl, 1:100 dilution) (Calbiochem, La Jolla, CA) was added to the sample to bind the primary antibody and incubated for 30 min at 4°C, followed by another wash with staining medium. Finally, streptavidin (50 μl, 1:100 dilution) conjugated with a fluorochrome (Cy5 dye covalently coupled to R-phycocerythrin (RPE-Cy5), was added (30 min at 4°C) to bind the secondary antibody (DAKO, Carpinteria, CA). The cells were incubated at 4°C for 30 min, washed with staining medium, and analyzed by flow cytometry. As a negative control, leukocytes were incubated in the same manner but without the primary antibody. As a specificity control for the prolactin-receptor antibody (U5), leukocytes were incubated with an isotype-matched, irrelevant IgG1 (200 μl, 10 μg; Becton Dickinson Immunocytometry Systems, San Jose, CA).

Results from previous studies indicated that the density of prolactin receptor per cell was different among the various leukocyte subpopulations (14). Our laboratory’s pilot experiments indicated high prolactin-receptor expression on B lymphocytes, one of the main target immune cells for prolactin (14, 26). Therefore, prolactin-receptor expression on B lymphocytes was measured by using dual labeling with a monoclonal antibody for CD19, a B-cell membrane molecule (Becton Dickinson Immunocytometry Systems) and U5. The cells were first incubated with U5 and the secondary antibody and then were incubated with a mouse IgG solution (50 ml, 1:100) to block any remaining sites on the goat anti-mouse secondary antibody. After another wash with staining solution, the cells were incubated (30 min 4°C) with an antibody for CD19 (5 μl) directly conjugated with a fluorochrome, phycoerythrin (PE). After incubation with the antibodies, analysis was performed with a flow cytometer (Epics XL-MCL, Coulter). The lymphocytes were gated on the basis of side scatter and forward-angle light scatter. The total number of B lymphocytes expressing prolactin receptors was calculated by multiplying the total B-cell concentration from the CBC by the percentage of B lymphocytes expressing prolactin receptor. The percentage of B lymphocytes (CD19+) expressing prolactin receptor (U5 positive) was determined from the flow cytometric histograms. The mean fluorescent intensity of the marker for prolactin receptor (RPE-Cy5) detected on B lymphocytes was used to compare the relative number of the prolactin receptors per B cell. Data were collected from analysis of 30,000 viable cells per sample.

Statistical Analyses

The data were analyzed by using a repeated-measures analysis of variance. Subsequent analyses were computed by using a Fisher’s least significant difference post hoc test. Tests for data outliers and assumptions for linear statistics were utilized, including tests for normality of distribution (Kolmogorov-Smirnov χ² test) and homogeneity of variance (Levene’s test), before analysis of variance. Those data sets failing any tests were diagnosed for the appropriate transformation procedure (log transformation was deemed appropriate), transformed, and retested for normality to meet the statistical assumptions. We used the Grubbs method for assessing outliers (also called the extreme studentized deviate procedure) showing that the value is unlikely to have come from the same Gaussian population as the other values in the group. Outliers were replaced with the remaining distributions mean score to maintain the response pattern and maintain needed statistical power viability. Statistical power was calculated ranging from 0.73 to 0.85 for the various dependent variables used in the study at the n size. The Pearson product-moment correlation was calculated to examine the relationship between prolactin-receptor expression and plasma prolactin concentrations. Statistical significance in this study was chosen to be P < 0.05.

RESULTS

Maximal Exercise Test

The mean duration of running on the treadmill was 13.6 ± 1.8 (SD) min. The mean maximum heart rate (194.4 beats/min) was very close to the age-predicted maximum heart rate (220 − 24.5 = 195.5 beats/min). The VO₂ max was 51.5 ± 7.4 ml·kg⁻¹·min⁻¹. One maximal exercise test for one subject was conducted without measuring his VO₂ max due to a problem with the O₂ or CO₂ analyzer. The mean ratings of perceived exhaustion (6 to 20 scale) at the final stage of the test (a few minutes before voluntary exhaustion) was 18.4 ± 0.9. In addition, the maximal exercise test significantly increased plasma lactate concentrations [F(1,7) = 1,532.7, P < 0.05; see METHODS]. Thus these data regarding heart rate, VO₂ max, ratings of perceived exhaustion, and plasma lactate concentrations indicated normal physiological responses to running on a treadmill at the high intensity.

Plasma Prolactin Concentration

The plasma prolactin concentrations increased significantly in response to exercise [F(1,7) = 16.2, P < 0.05] (Fig. 1). The concentration postexercise was also significantly greater than the postexercise control value. There was no significant difference in the concentration between preexercise and preexercise control blood samples. To account for the potential hemocon-
centrating effects of exercise-induced plasma volume shifts, the prolactin concentration data were also adjusted to the plasma volume change (16). This correction did not change the relative outcome.

**Total Circulating Lymphocytes**

The maximal exercise test significantly increased the total blood lymphocyte concentration by nearly threefold on average \( F(1,7) = 112.9, P < 0.05 \); Table 1. This increase was not seen in the blood of the resting, control subjects. Similarly, the B-lymphocyte subset of the total lymphocytes also increased significantly \( F(1,7) = 8.7, P < 0.05 \); Table 1. These increases remained significant even after the values were corrected for blood volume changes due to exercise (data not shown).

**Prolactin-Receptor Expression**

Approximately 70% of the B lymphocytes expressed prolactin receptors (Table 2). This percentage was not significantly affected by exercise \( F(1,7) = 3.9, P > 0.05 \). However, the total number of circulating B lymphocytes expressing prolactin receptor significantly increased in response to the exercise \( F(1,7) = 10.8, P < 0.05 \); Table 2] from \(-100\) to \(200\) cells/ml of blood. Even after the values were corrected for blood volume change due to exercise, the increase remained significant (data not shown). Moreover, the total number of prolactin receptors expressed per B lymphocyte also significantly increased after exercise (\( P < 0.05 \); Fig. 2). The total prolactin-receptor expression per B lymphocyte increased by \(-30\%\) compared with preexercise and to postexercise control samples.

Prolactin receptors were also detected on a small portion (\(-4\%)\) of non-B (CD19\^-\) lymphocytes, which presumably were T lymphocytes and NK cells (Table 3). The effect on the exercise on the prolactin receptor expression of these CD19\^-\) lymphocytes was not statistically significant \( F(1,7) = 2.5, P > 0.05 \). Because the subset-specific monoclonal antibodies (CD3 for T cells, CD56 for NK cells) were not used in this study, no further analyses were conducted.

**Correlation Between Prolactin-Receptor Expression and Plasma Prolactin Concentration**

There was a significant positive correlation between total prolactin-receptor expression per B lymphocyte and plasma prolactin concentrations (\( r = 0.495, P < 0.05 \); Fig. 3). In addition, the change in total prolactin-receptor expression per B lymphocyte between preexercise and postexercise blood samples correlated significantly with the change in the plasma prolactin concentrations (\( r = 0.525, P < 0.05 \)). Even after correction for plasma volume change, the total prolactin-receptor expression per B lymphocyte significantly correlated (\( r = 0.480, P < 0.05 \)) with the plasma prolactin concentrations.

On the other hand, the plasma prolactin concentration did not significantly correlate with the total number of circulating B lymphocytes (\( P > 0.05, r = 0.254 \)) or with the number of B lymphocytes expressing the prolactin receptor (\( P > 0.05, r = 0.264 \)). These results did not change after correction for hemococoncentration.

**DISCUSSION**

The present study provides an analysis of prolactin-receptor expression on human lymphocytes in response to exercise stress. The primary findings are that the total prolactin-receptor expression per B lymphocyte as well as plasma prolactin concentration increased in response to acute aerobic exercise. In addition, exercise significantly increased the total number of circulating B lymphocytes expressing prolactin receptor.

Although the exact mechanisms of regulation of prolactin-receptor expression during exercise remain to be determined, one possibility is that it is upregulated by prolactin itself. Evidence from animal studies supports this possibility (3, 37). Elevations in prolactin upregulated prolactin-receptor expression by the target cells of liver, lung, brain, and hypothalamus (2, 30, 37). In

### Table 1. Total circulating lymphocytes and B lymphocytes

<table>
<thead>
<tr>
<th></th>
<th>Total Lymphocytes</th>
<th>Total B Lymphocytes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Preexercise</td>
<td>Postexercise</td>
</tr>
<tr>
<td>Exercise session</td>
<td>1,581 ± 423</td>
<td>4,900 ± 1,058*</td>
</tr>
<tr>
<td>Control session</td>
<td>1,719 ± 259</td>
<td>1,835 ± 353</td>
</tr>
</tbody>
</table>

Values are means ± SD given as \(\times 10^9\) cells/ml blood. Total lymphocytes and total B lymphocytes were determined by flow cytometry and complete blood counts as described in METHODS. *Significantly different from preexercise and from postexercise control, \( P < 0.05 \).

### Table 2. Prolactin-receptor expression of circulating B lymphocytes

<table>
<thead>
<tr>
<th></th>
<th>B Lymphocytes Expressing Prolactin Receptor, %</th>
<th>Total Number of B Lymphocytes Expressing Prolactin Receptor, (\times 10^9) cells/ml blood</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Preexercise</td>
<td>Postexercise</td>
</tr>
<tr>
<td>Exercise session</td>
<td>75.2 ± 10.6</td>
<td>68.6 ± 9.9</td>
</tr>
<tr>
<td>Control session</td>
<td>72.2 ± 19.9</td>
<td>71.5 ± 16.7</td>
</tr>
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Values are means ± SD. *Significantly different from preexercise, \( P < 0.05 \).
general, these studies were based on exogenous administration of prolactin (30), the use of surgical procedures (37), or the use of chemicals such as haloperidol to increase prolactin (28). In only one published study were the effects of prolactin elevation on prolactin-receptor expression by human leukocytes reported (26). This study indicated no significant difference in prolactin-receptor expression between hyperprolactinemic and normal subjects. However, chronic prolactin elevation at rest is likely different from an acute increase in prolactin through physical exercise by the healthy population in the present study. Moreover, Clodi et al. (11), who examined cytokine production and NK cell activity of hyperprolactinemic patients with pituitary tumors, found that chronically elevated serum prolactin concentrations induced adaptation and abolished the acute immunostimulatory effects of prolactin. Therefore, acute prolactin elevation may increase prolactin-receptor expression by immune cells even though persistent acute prolactin elevation may not. In the present study, there was a significant positive correlation between plasma prolactin concentrations and total prolactin-receptor expression per B lymphocyte, although correlational analysis cannot establish causation.

Another possible mechanism of exercise-induced prolactin-receptor expression may be mediated through cortisol, which is known to be immunosuppressive (13). High-intensity exercise is well known to increase cortisol concentrations (22). Oleshansky et al. (34) indicated that cortisol elevation is related to the relative intensity of exercise regardless of subjects’ physical fitness levels. Thus, in this study during the maximal exercise test, increased prolactin may counteract the effects of glucocorticoids to maintain immune homeostasis.

It has been suggested that the physiological impact of both prolactin and glucocorticoids during stress is regulated through receptor interaction on the target cells (6). Berton and Dave (6) reported that the administration of exogenous corticosterone to mice reduced both lymphocyte proliferation as well as prolactin binding to the liver. However, after prolactin administration, the liver prolactin-receptor expression and lymphocyte proliferation increased. These results suggest the importance of prolactin-receptor expression in the regulation of cell function.

**Table 3.** Prolactin-receptor expression on non-B lymphocytes

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<thead>
<tr>
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<th>Preexercise</th>
<th>Postexercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>16.1 ± 6.1</td>
<td>20.5 ± 4.8</td>
</tr>
<tr>
<td>Control</td>
<td>17.1 ± 5.2</td>
<td>17.8 ± 6.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. Results represent mean fluorescence intensity of the marker (Cy5 dye covalently coupled to R-phycoerythrin) for prolactin receptor on non-B lymphocytes, which is proportional to the relative number of prolactin receptors per cell.
In the present study, prolactin receptor was also expressed on a small portion of non-B lymphocytes (CD19+), T lymphocytes, and NK cells. Although the effect of exercise on prolactin-receptor expression on these CD19+ lymphocytes did not reach statistical significance at the P < 0.05 level, the analysis may not be precise because each specific subset of cells was not examined. Future studies will be necessary to determine the effects of exercise on prolactin-receptor expression on other lymphocytes, NK cells, and monocytes.

Although the present study did not include sequential blood sampling during the recovery period, the elevation of plasma prolactin has been shown to return to the baseline within 1 h after exercise (23, 27). It is unknown how long the increased prolactin-receptor expression on B lymphocytes continues. If the immunostimulatory function of prolactin and its half-life of 15–20 min are considered, exercise-induced elevation of prolactin is consistent with a promotion in immune cell function. Animal studies by Ortega et al. (35) support this possible relationship. They demonstrated that acute aerobic exercise increased the plasma prolactin concentration as well as the phagocytic activity of macrophages in mice. Furthermore, previous studies with humans have demonstrated that there is an enhancement of antibody production or serum Ig concentrations in response to acute aerobic exercise (19, 32, 36). Although these investigators did not analyze prolactin, its presence is consistent with the elevations of serum immunoglobulin in response to acute exercise. Because of its immune-enhancing property, prolactin has been considered as a therapeutic agent for immune-deficient patients, including those undergoing bone marrow transplant and radiation/chemotherapy (4, 39). In addition, hormone therapy may be useful for slowing a decline in the immune and other systems during aging (17, 29). Although most animal studies have investigated prolactin in connection with surgical, chemical, and mechanical stress, the present study demonstrates a possible relationship between prolactin and human immune cells in response to exercise. Thus one of the positive effects of physical exercise may include an increase in endogenous prolactin especially for patients with a deficiency in the immune system.

In summary, the present study demonstrated that acute aerobic exercise elevated plasma prolactin concentrations and the total number of circulating B lymphocytes expressing prolactin receptor. In addition, there was an increase in total prolactin-receptor expression per B lymphocyte in response to exercise. Furthermore, B-cell prolactin-receptor expression was positively correlated with plasma prolactin concentrations. Thus this study supports the idea that physical exercise may enhance the interaction between human immune target cells and prolactin, a hormone capable of stimulating the immune function. The knowledge of exercise-induced immunoregulation may facilitate our total understanding of the intercommunication between endocrine and immune systems.

We thank Drs. William Buckley, Craig Denegar, and Jay Hertel for assistance in this investigation. We sincerely appreciate Dr. Mireille Dardenne for providing the U5 prolactin-receptor monoclonal antibody. We express our gratitude to Elaine Kunze for technical support in flow cytometric analysis and to Ana Gomez, Mickey Rubin, and Jennifer Jewell for assistance in the plasma assays. We also express our gratitude to the dedicated subjects who participated in this investigation.

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